Kobbernagel and colleagues have demonstrated that the course of PCD lung disease can be improved using a widely available and relatively low-cost pharmacological treatment. Indeed, lung function remained unchanged over the intervention period, and a treatment beyond 6 months is needed to evaluate the efficacy in this field. In one study, FEV_1 decline among several patients with cystic fibrosis in a French Registry appeared less marked after than before prolonged azithromycin treatment initiation.[9] However, in that non-randomised, retrospective study the decision to start long-term azithromycin was based on a pre-treatment FEV_1 level that was quite low, thus more sick patients with cystic fibrosis were included. This factor is a striking difference with the BESTCILIA trial that ruled out PCD patients with more severe pulmonary disease.

Kobbernagel and colleagues are to be congratulated for this well designed study including a large number of patients, which is difficult to achieve in rare disorders. The participating centres are members of either the European Reference Network on respiratory diseases or the Better Experimental Approaches to Treat PCD network.[10,11] The role of networks for uncommon diseases is crucial to improve access of patients to diagnosis and treatment, and to encourage collaborative research from different countries.

Future directions for research on treatment of PCD airways infections should include longer prospective clinical trials, the recruitment of patients with more impaired lung function and those with *Pseudomonas* spp colonisation. Comparative studies with prophylactic nebulized or intermittent systemic antibiotics are also necessary. The PCD community is confident that BESTCILIA is only the first of a series of future multicentre clinical trials that will provide more guidance for precision medicine for the PCD population.

FS is member of Better Experimental Approaches to Treat PCD (COST Action 1407), and the affiliated Department is part of the European Reference Network on respiratory diseases. All other authors declare no competing interests.

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Understanding pathways to death in patients with COVID-19

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Since the first cases of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), were identified in China in December, 2019, we have witnessed increasing numbers of infections and associated deaths worldwide. Although the case fatality rate for SARS-CoV-2 infection (ie, the total number of deaths in patients positive for SARS-CoV-2 divided by the total number of people with a positive test) is not high, given the huge scale of the pandemic, the actual numbers of deaths are considerable.

In *The Lancet Respiratory Medicine*, Jason Phua and colleagues[1] provide an excellent overview of the current issues raised by COVID-19—in particular, the impact of the disease on intensive care. The Review is clearly and comprehensively written, covering many aspects of the

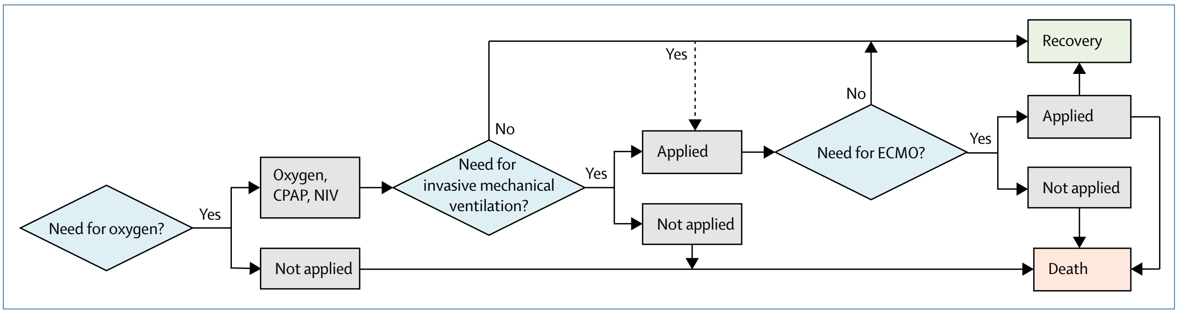

***Figure:* Possible paths to death and recovery in patients needing respiratory support**
CPAP=continuous positive airway pressure. ECMO=extracorporeal membrane oxygenation. NIV=non-invasive ventilation.

disease, from epidemiology and diagnosis through to intensive care treatment and resource management. One issue raised by this Review is how the reported case fatality rates for patients with COVID-19 can be accurately interpreted.

Currently reported case fatality rates vary from 1% to more than 7%,[2] but these values must be interpreted with caution. For example, where massive screening has been performed in the whole population (eg, in South Korea and Switzerland), overall case fatality rates of less than 1% have been reported, because the denominator included many mild or asymptomatic cases. However, in countries where only people requiring hospital admission are being screened (eg, Italy and Spain), case fatality rates have exceeded 5%, because the denominator is much smaller.

The actual cause of death is also important in interpreting case fatality rates. Respiratory failure is obviously the main cause,[3] as was also the case in previous viral pandemics, such as the Spanish flu of 1918. Today, however, many patients can be supported by invasive mechanical ventilation until the lungs recover. If the situation deteriorates, use of extracorporeal membrane oxygenation (ECMO) systems can control gas exchange for weeks. COVID-19 is sometimes complicated by shock and multiple organ failure,[4,5] but the real course of the disease is not yet well described. Knowing that non-survivors are more likely to have low lymphocyte counts or high C-reactive protein or D-dimer levels[3,6,7] provides no information about the actual process of death. The precise role of secondary bacterial infections has also not been well defined.

Ethical issues also have a relevant role in interpreting case fatality rates, especially when the elderly and frail are more at risk and when resources are stretched so that some form of rationing or triage might become necessary. In such a scenario, differentiating whether the cause of death is specifically due to COVID-19 or the result of treatment limitations can be difficult. Among patients who die before reaching the hospital, some will present too late in the course of the disease to be saved, whereas end-of-life care will be viewed as preferable for others because little chance of survival with a meaningful quality of life exists. In some patients, this decision might be influenced by known individual preferences. Similarly, not all critically ill patients in hospital will be admitted to the intensive care unit (ICU), because the chances of meaningful survival for some will be viewed as too low;[8] for these patients, non-invasive

Panel: Three possible characteristics of the dying process in COVID-19

Predominant terminal organ failure
- Terminal respiratory failure: mechanical ventilation and ECMO used
- Terminal respiratory failure: mechanical ventilation used, ECMO available but not used
- Terminal respiratory failure: mechanical ventilation used, ECMO not available
- Respiratory failure: mechanical ventilation available but not used
- Respiratory failure: mechanical ventilation hardly or not available
- Septic shock, multiple organ failure
- Cardiogenic shock (acute myocardial injury or myocarditis)
- Other

Proportionality of care in the dying process
- Withholding life support: life support available but considered to be disproportionate; life support hardly available (significant constraints)
- Withdrawing life support
- Full care but no cardiopulmonary resuscitation
- Full care including cardiopulmonary resuscitation

Involvement of COVID-19 in the dying process
- Death attributed only to COVID-19 (previously healthy, predicted long life expectancy)
- Death primarily due to old age, frailty, or advanced disease (COVID-19 is an epiphenomenon)
- Death due to COVID-19 in an individual with limited life expectancy

COVID-19=coronavirus disease 2019. ECMO=extracorporeal membrane oxygenation.

ventilation and perhaps even some vasopressor support could be provided in so-called middle care units, but in case of further deterioration, mechanical ventilation will not be considered and death will occur because of severe hypoxaemia. As noted by Phua and colleagues,[1] a quarter of patients who died early in the Wuhan, China, outbreak did not receive invasive ventilation.[9] Patients who deteriorate despite mechanical ventilation can be placed on resource-intensive ECMO systems (figure).[10] The decision not to use ECMO might be made because the support system is not available or because such care is considered to be disproportionate in the context of limited staff numbers. The same considerations might apply to patients who develop renal failure. Use of renal replacement therapies is uncommon in those with COVID-19,[4,6,7] although acute kidney injury might occur in a third of patients.

Several different scenarios can thus be considered when interpreting deaths from COVID-19. First, for patients admitted to the ICU, death might occur despite full intensive care support, including mechanical ventilation, ECMO, vasopressors, and renal replacement therapy. On modern ICUs, such deaths are expected to be infrequent; however, robust estimates of the number of deaths cannot be made from the mostly descriptive reports currently available. A second possible scenario for ICU and hospital patients is related to limitation of life-sustaining therapies because of poor predicted outcomes associated with old age, frailty, comorbidities, or profound disability, or because of effects of distributive limitations associated with lack of personnel, beds, or materials. A combination of these two factors often exists. A third scenario relates to patients admitted to the ICU or hospital whose deaths are not directly related to COVID-19. Especially in areas with high infection rates, patients might be admitted to the ICU with, for example, severe trauma or acute brain injury, test positive for SARS-CoV-2 during the ICU stay, and eventually die because of the initial injury; these deaths will still be attributed to COVID-19 and included in the statistics. Similarly, some patients might have SARS-CoV-2 infection, but the actual contribution of the virus to the patient's death might be minimal. For example, in a patient with metastatic cancer or terminal organ failure, is the viral infection or the patient's underlying condition the cause of death? The actual role of SARS-CoV-2 infection in such deaths is particularly difficult to evaluate in countries where only one cause can be reported on a death certificate.

To be able to better interpret case fatality rates, more data are thus needed (panel). First, the type and severity of organ failure: what are the real contributions of respiratory or cardiovascular failure? How many patients died with isolated respiratory failure, in shock or with acute kidney injury or multiple organ failure? Second, the actual process of death, including therapeutic limitation when present and the relative contributions of patient factors (eg, age and comorbidities) or environmental factors (eg, lack of facilities, beds, personnel, or equipment). Last, the real contribution to death of SARS-CoV-2 infection, because COVID-19 can be an epiphenomenon in some patients.

We have learnt a lot in a relatively short period of time, and the Review by Phua and colleagues[1] summarises this knowledge well. However, we still have a lot to learn. Among the many unanswered questions is the key issue related to the actual process leading to death. Global numbers of deaths and case fatality rates provide only crude information.

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